REMARKS

This Reply is fully responsive to the final Office Action mailed on July 12, 2005. Reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with the remarks which follow are respectfully requested.

At the outset the Examiner is respectfully thanked for the recent personal interview held on October 12, 2005 with the undersigned, Examiner Landsman, and Dr. Mark Zoller, the Chief Scientific Officer at Senomyx Inc. the Assignee of this application, and an inventor on this patent application. During the interview all of the outstanding rejections which based on 112 first paragraph enablement and written description grounds were discussed in detail. Particularly Applicants argued that the claims directed to nucleic acid sequences encoding polypeptides exhibiting at least 90% sequence identity to the exemplified human T1R2 polypeptide are adequately enabled and described by the teachings of the application. Specific reference was made to a PowerPoint Presentation by Mark Zoller which made reference to a publication which contains data establishing that chimeric T1R2 polypeptides exhibiting as low as about 80% sequence identity to the subject T1R2 polypeptides have been shown to be active (respond to natural and artificial sweet compounds in assays such are are disclosed in the subject patent application). As requested by the Examiner this PowerPoint Presentation is attached as an Exhibit to this Response. Additionally, it was noted during the interview that the underlying data relating to such chimeric T1R2 proteins and other chimeric T1R polypeptides as is contained in Xu et al,

Proc. Natl. Acad. Sci., U.S.A (see PowerPoint citation to this article.) As further noted, Proc. Natl. Acad. Sci., U.S.A., is a well accepted peer-reviewed journal.

Also, Applicants argued that the expression of the subject hT1R2 sequence in association with G proteins other than the promiscuous G protein exemplified in the subject application is also enabled and adequately described by the teachings of the application as evidenced by the relevant state of the art. It was noted that the subject Galpha15 protein was selected in large part because of its promiscuous nature and further based on the fact that the present Assignee has an exclusive license relating to the use of this particular G protein in screening assays using taste and olfactory GPCRs. However, it was noted that many G proteins are widely available that also potentially could and have been used including for example Galpha16, transducin, gustducin and chimeras thereof. Moreover, Applicants noted that the present Assignee has also found that Gi proteins functionally couple to the subject T1R taste receptors and has a corresponding patent application, US Serial No. 10/770,127 recently allowed..

Finally, Applicants noted that the Present Assignee recently obtained an allowance in US Serial Number 09/897,427 (now U.S. Patent No. 6,955,887) which contains claims of similar scope to those being pursued herein (claims in this now-patented application encompass co-expression of hT1R3 and a hT1R2 nucleic acid sequence encoding a T1R2 polypeptide exhibiting at least 90% sequence identity to an exemplified hT1R2 polypeptide sequence as herein. Applicants further argued at the interview that the withdrawal of the

outstanding 112 rejections would further seem appropriate in the interest of consistent prosecution in these related cases.

Based on these arguments, and the supporting PowerPoint Presentation the Examiner seemed favorably disposed but indicated that he would need to have the case reviewed and any decision on allowability would need to be approved by a Supervisory Examiner. Further, Applicants indicated at the interview that the response to the Final Rejection would be submitted with an RCE Request to afford the Examiner the necessary time and flexibility to resolve issues of patentability in this application. The undersigned stressed the great importance of the subject matter being pursued in this patent application to the present Assignee Senomyx Inc. and its licensees.

Turning now to the most recent Office Action, Claims 235 and 237-267 stand rejected under 112 enablement and description grounds on two separate bases:

(i) artificially constructed hT1R2 nucleic acid sequences encoding hT1R2 polypeptides possessing at least 90% sequence identity to the exemplified hT1R2 polypeptide sequence contained in SEQ ID NO:20 allegedly are not adequately enabled and/or described by the teachings of the as-filed patent application; and

(ii) the expression of hT1R2 in association with G proteins other than the exemplified promiscuous G protein Galpha15 allegedly is not enabled and/or described by the teachings of the as-filed patent application.

Based on the foregoing, and for substantially the same reasons enumerated at the recent interview these rejections are respectfully submitted to be factually and legally unsustainable and therefore should be withdrawn. Also, these rejections should be withdrawn as they are inconsistent with the Patent Office's disposition of a related patent application, US Serial No. 09/897,427 now patented. The enablement and written description rejections are addressed together herein as the issues in both rejections are highly related .

With respect to the 112 enablement and written description rejections, at the outset Applicants concede the fact that the claims encompass variants of the exemplified hT1R2 polypeptide, which are constructively enabled and described by the teachings of the as-filed patent application, but which are not actually reduced to practice in the application the form of specific variants demonstrated to retain the same functionality (sweet ligand binding properties) as the exemplified hT1R2 polypeptide. However, Applicants respectfully maintain that practice of the full scope of the claims would not require undue experimentation and further that the teachings of the subject application would place the skilled artisan in possession of screening assays that would readily facilitate the identification and selection of hT1R2 variants exhibiting at least 90% sequence identity to the exemplified hT1R2 polypeptide which are functional (i.e., variants which specifically bind sweet ligands).

Applicants emphasize that this is NOT an orphan receptor type situation. To the contrary the teachings of this application illustrate that the subject

hT1R2 specifically responds to and binds in accepted GPCR assays to a plurality of both sweet and artificial sweet compounds.

Based on this fact, it would be routine too reproduce such assays with variant hT1R2 sequences falling within the limited genus of sequences encompassed by the present claims and ascertain those of which are functional, i.e., specifically bind and/or respond to sweet ligands. The routine and predictable nature of this screening method is supported by the ready availability of numerous sweet ligands and accepted GPCR in vitro screening assays.

The rejection is further unsustainable because, as explained by the inventor, Dr. Zoller, the subject T1R2 receptor is a member of a well characterized subgenus of GPCR proteins, which have been well characterized and which share related and conserved domain structure supporting a conclusion that a skilled artisan would be aware of what specific residues likely impact ligand binding and those of which may be modified without detrimental effects on ligand binding properties of the resultant hT1R2 variant. In factual support of this argument Dr. Zoller made specific reference to a number of hT1R2 variants (chimeras) which have been later constructed by the subject Assignee and which have shown to be active (bind sweet ligands) (See attached Powerpoint Presentation and Xu et al. (2004) PNAS publication cited therein which also contains the underlying data). This data provides compelling evidence that a skilled artisan would be able to construct hT1R2 variants that fall within the scope of the claims and confirm in ligand binding assays that these variants are

functional. (In fact these experiments showed that T1R variants possessing as low as 80-85 sequence identity to a corresponding wild-type T1R sequence could be obtained which are functional.) Also, these experiments support Applicants' arguments that the Hoon et al. article is not applicable to the facts herein since this article predates the ligand binding and experimental results contained in this patent application. Particularly, once it had been shown that a particular GPCR (hT1R2) responds to specific ligands in assays, and may be expressed in functional form in vitro, as is shown in the subject application, it is well within the level of skill to synthesize and select variants that retain similar properties using these same expression methods, assays and ligands. Indeed the experimental evidence submitted herein and discussed at the interview is proof of this fact.

Aside from the rejection being factually unsustainable, Applicants further respectfully submit that it is legally unsustainable as well. The attention of the Examiner is respectfully directed to a recent Board of Appeals Decision, Ex parte Bandman, No. 2004-2319 (BPAI 2005) wherein the Board reversed a similar 112 enablement and written description rejection wherein the Appellant was claiming variants encoding polypeptides exhibiting at least 95% sequence identity to an exemplified wild-type sequence. As is the case herein, the protein at issue possessed a known (enzymatic) activity that could be screened for in reproducible assays. The Board in their decision did not speak directly to the potential enablement or written description issues raised by claiming sequences that possess at least 90% rather than 95% sequence identity to an exemplified

wild-type sequence (shown to possess a function that may be screened for in appropriate assays). However, the decision in Bandman is still believed to be on point especially given the fact that the subject Applicants have submitted convincing evidence showing that variants possessing less than the sequence identity recited in the claims may be constructed which are functional. Indeed, had similar evidence been of record in Bandman, it is likely that the Board would have concluded that claims of similar scope to those being pursued herein meet the 112 written description and enablement requirements.

Also, in its decision the Board also relied on the Federal Circuit decision in Enzo Biochem, Inc v. Gen-Probe Inc., 296 F.3d 1316 (Fed. Cir. 2002). Further, the Board specifically indicated in its decision that meeting the enablement and written description requirement does not require that the specification provide specific guidance as to which amino acid residues (in protein to be mutated) are tolerant to change. Rather, they concluded that the skilled artisan could identify those residues absent undue experimentation because the methods and information in the application would place the skilled artisan in possession of appropriate screening methods. The facts herein are directly analogous to those in Bandman. Based on the foregoing, Applicants respectfully submit that the 112 enablement and written description rejection based on the claims encompassing hT1R2 variants should be withdrawn as these rejections are factually and legally unsustainable.

The other basis of the 112 enablement and written description rejection of claims 235 and 237-267 relates to the selection of G proteins other than

Galpha15). Specifically, the Examiner concluded that the teachings of the as-filed application only enabled and placed a skilled artisan in possession of expression methods wherein hT1R2 is expressed in association with the exemplified G protein. This rejection is further respectfully traversed and should also be withdrawn as it is unsustainable.

As explained at the recent personal interview, Galpha15, while exemplified in the working examples of this application is not essential to the operability of the invention. Indeed this G protein was largely selected simply because the present inventors have much experience expressing this G protein in association with this and other GPCRs including other taste receptors. However. as explained, T1Rs have been functionally expressed in association with various other G proteins known and widely available as of the date of invention including by way of example Galpha16, various Gi proteins, transducin, gustducin as well as chimeras thereof.

In fact, various later-filed patent applications by the present Assignee and subsequent publications support Applicants' argument. For example, Applicants recently received an allowance in commonly assigned US Serial No. 10/770,127 directed to assays involving the functional coupling of T1Rs and T2Rs to various Gi proteins. Therefore, Applicants respectfully submit that the selection of other G proteins suitable for use in the claimed invention is both enabled and described by the teachings of this patent application.

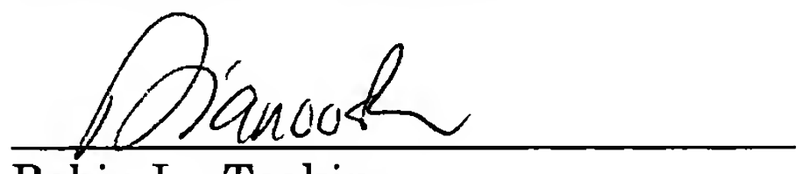
Based on the foregoing, these amendments and remarks should place this application in condition for allowance. A Notice to that effect is respectfully requested.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 04-1679 (Docket #100337.54289US).

Respectfully submitted,

December 12, 2005



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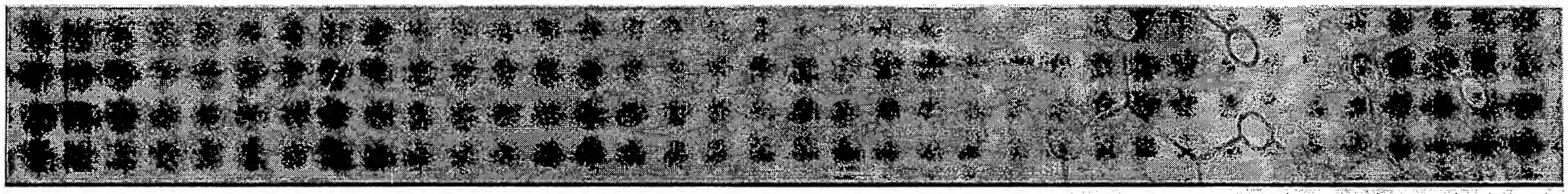


Senomyx Presentation to Patent Office

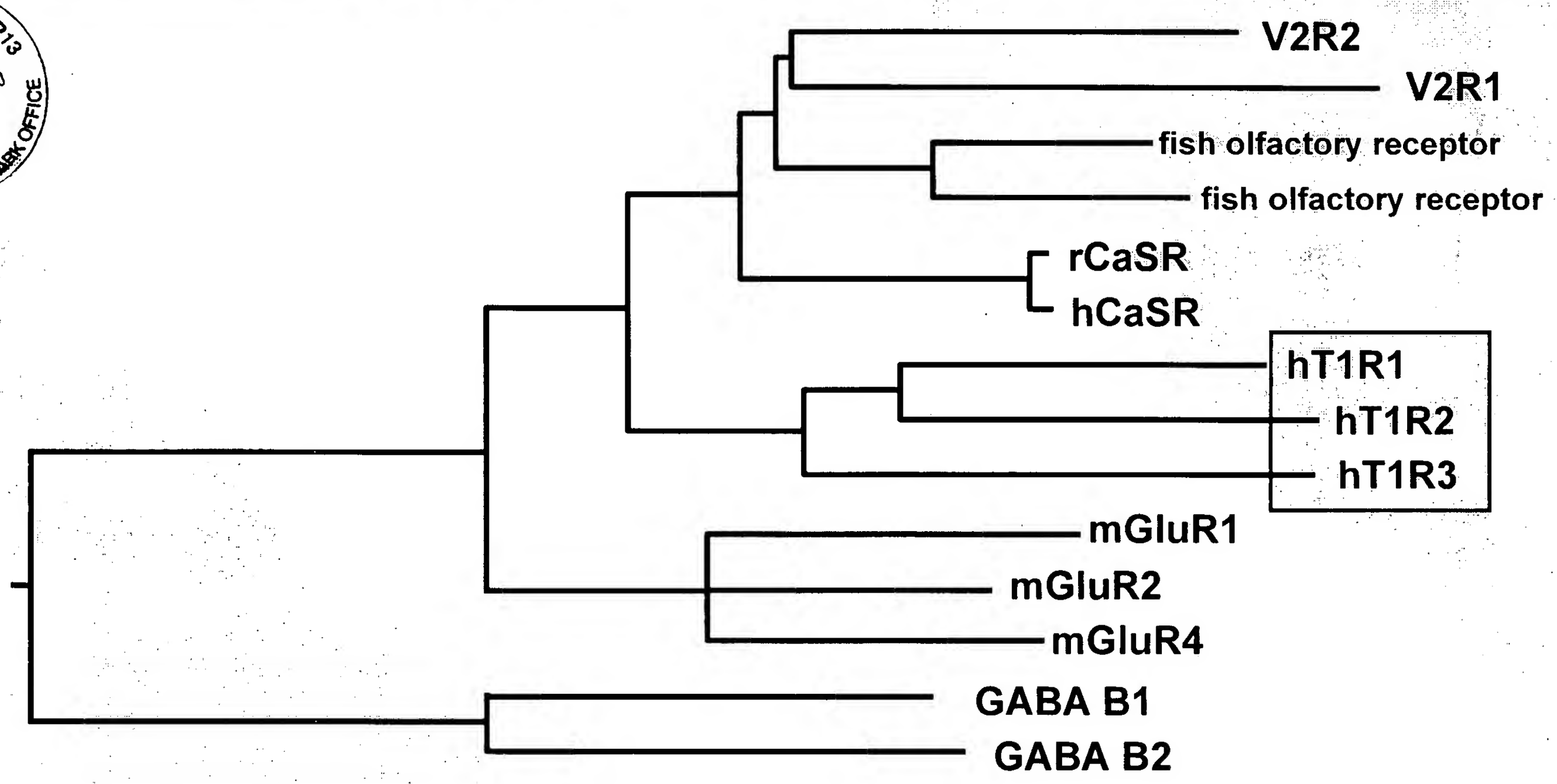
Mark Zoller

Chief Scientific Officer

October 12, 2005

Senomyx, Inc.

T1Rs Belong to the Class C Family of GPCRs

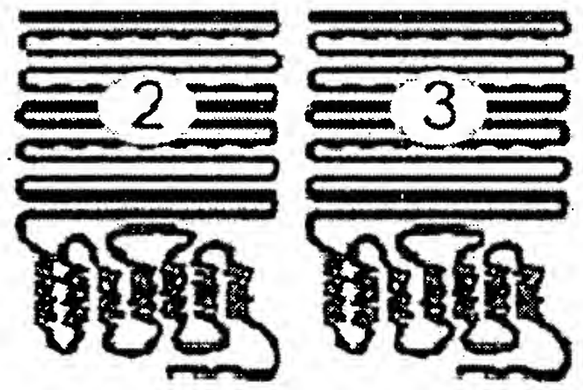


mGluRs function as homodimers (Kunishima 2000)

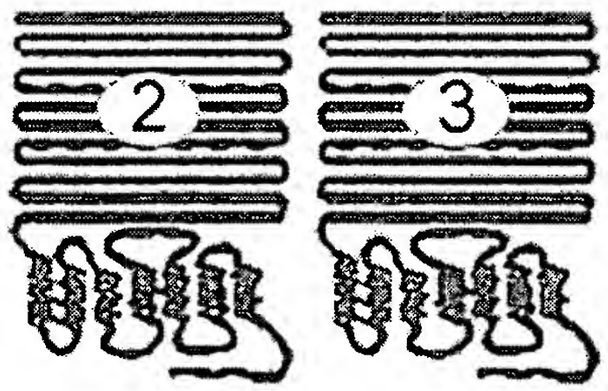
GABA B receptors known to form heterodimers (Kaupmann 1998)

Dissecting T1R Ligand Binding Using Human-Rodent Chimeric Receptors

Native Receptors

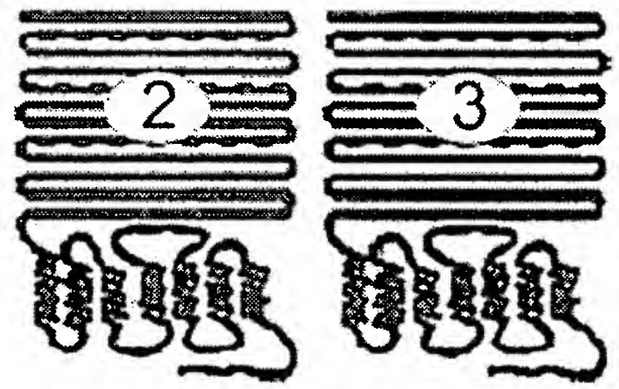


Human T1R2/T1R3

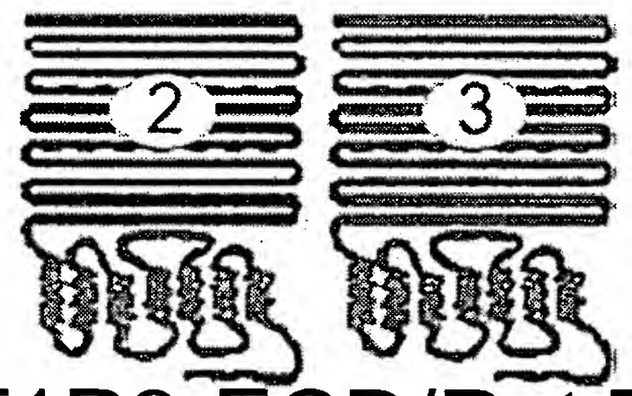


Rat T1R2/T1R3

Chimeric Receptors



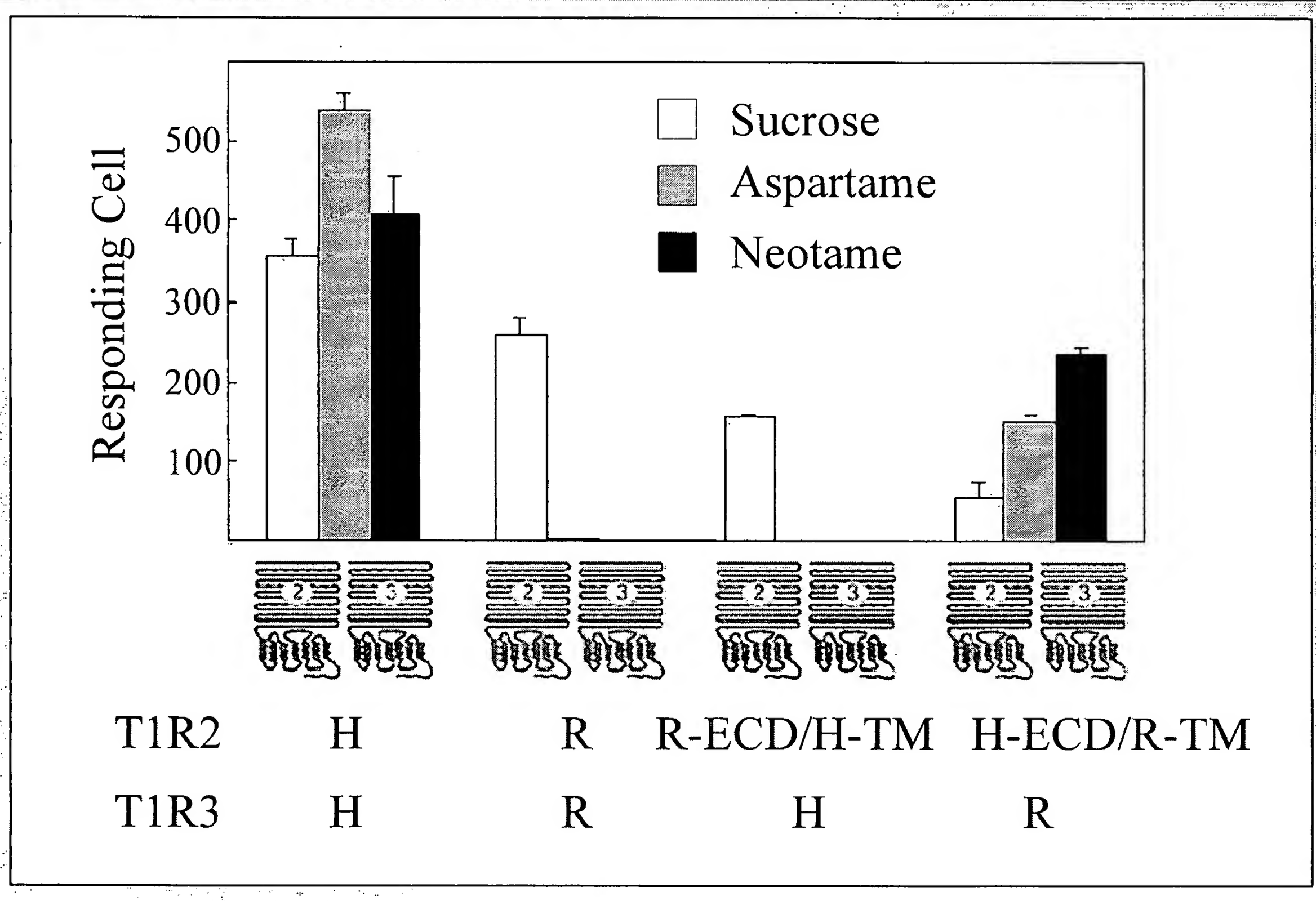
Rat T1R2-ECD/Human T1R2-TM
HUMAN T1R3
(~95% identical to human)



Human T1R2-ECD/Rat T1R2-TM
Rat T1R3
(~85% identical to human)

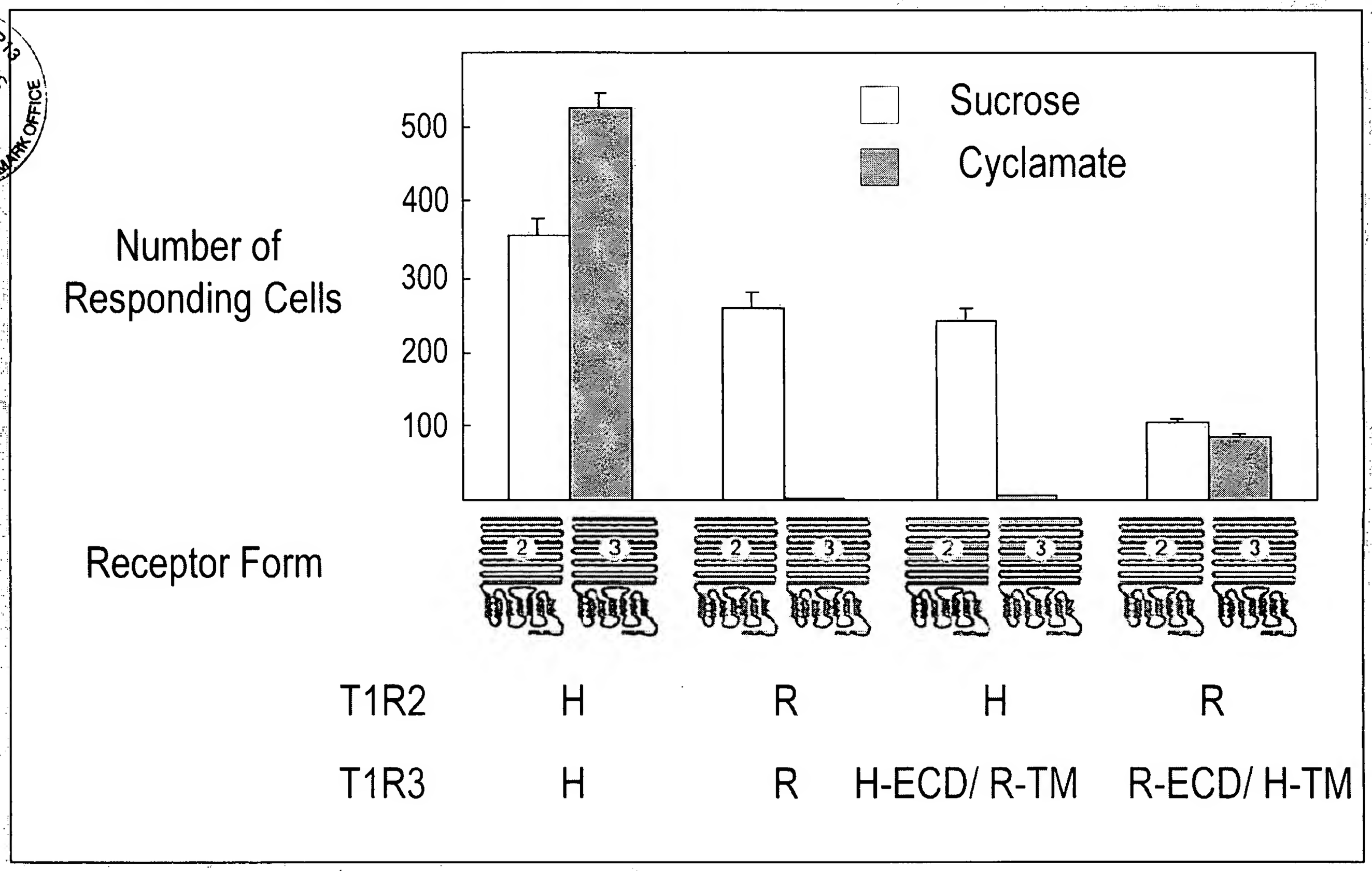
ECD = Extracellular Domain

Aspartame and Neotame Map to T1R2



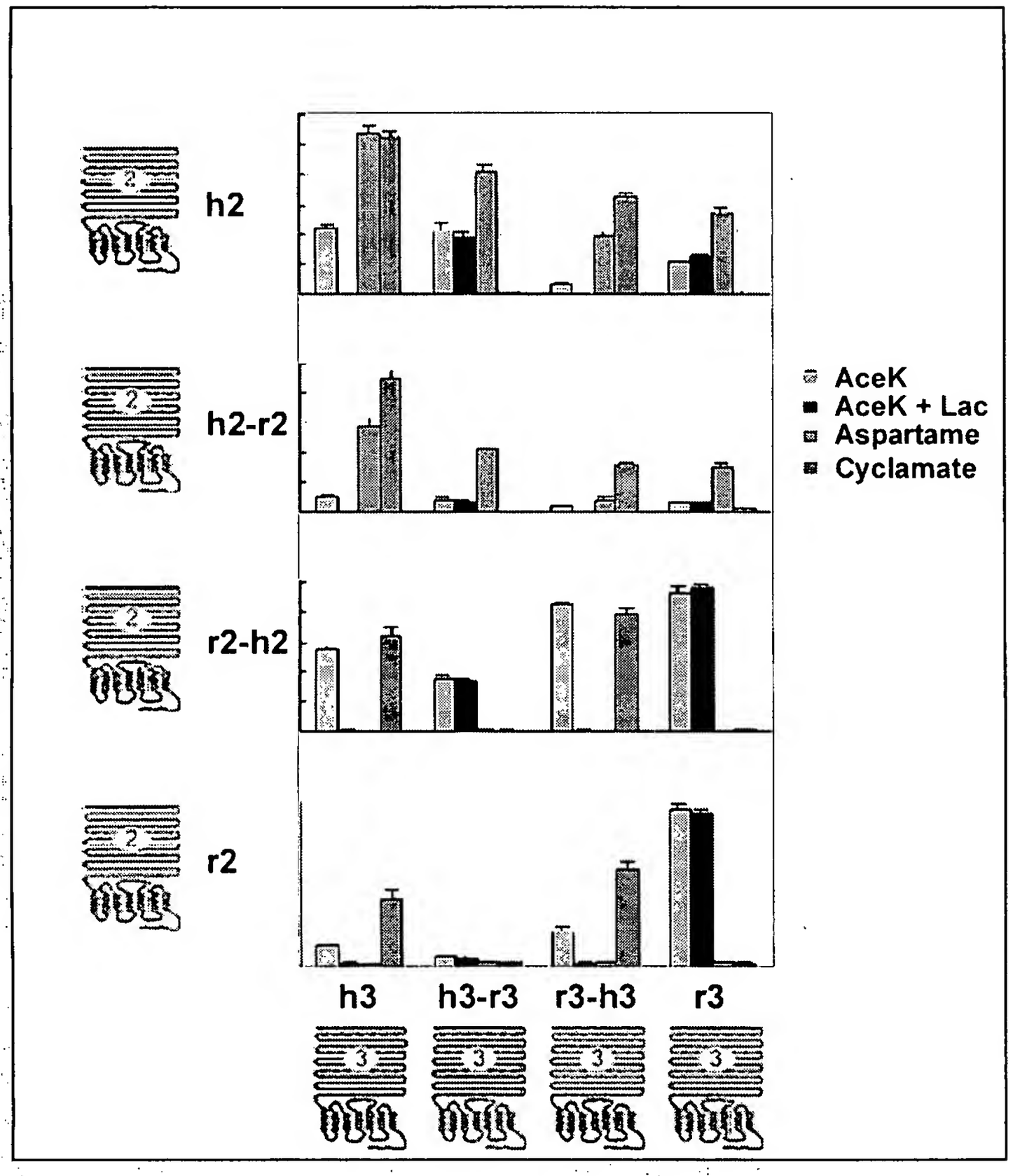
Senomyx, Inc.

Activation by Cyclamate Requires Human T1R3 Transmembrane Domain



Senomyx, Inc.

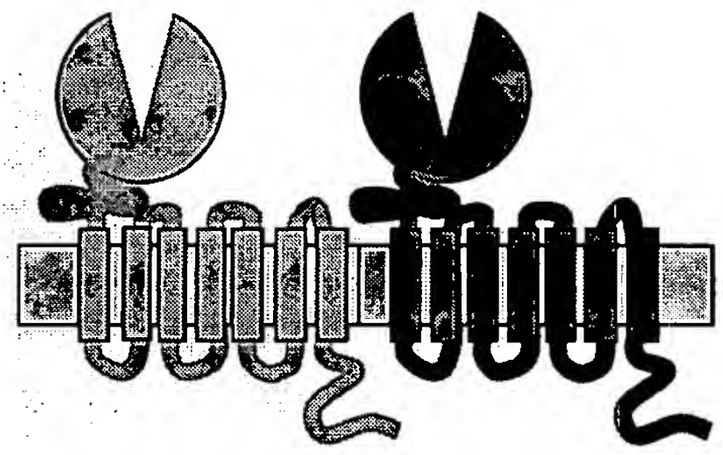
Additional Combinations of T1R2/T1R3 Human-Rodent Chimeras



Senomyx, Inc.

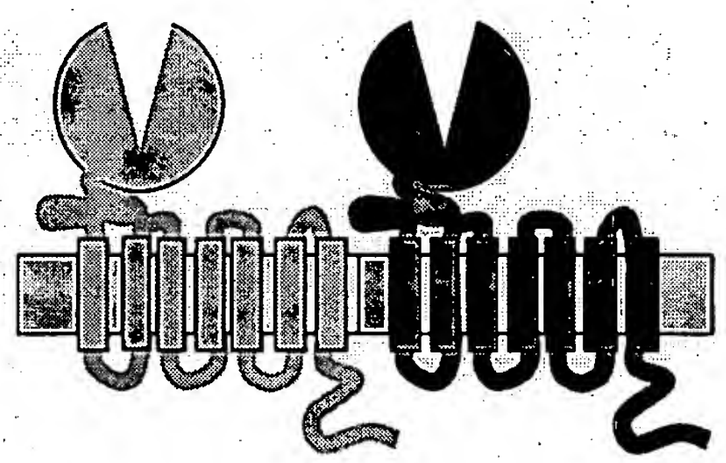
Cyclamate is an Enhancer of Aspartame on a Human Receptor with T1R2-ECD/T1R1-TM + T1R3

T1R2 T1R3



Sweet Receptor

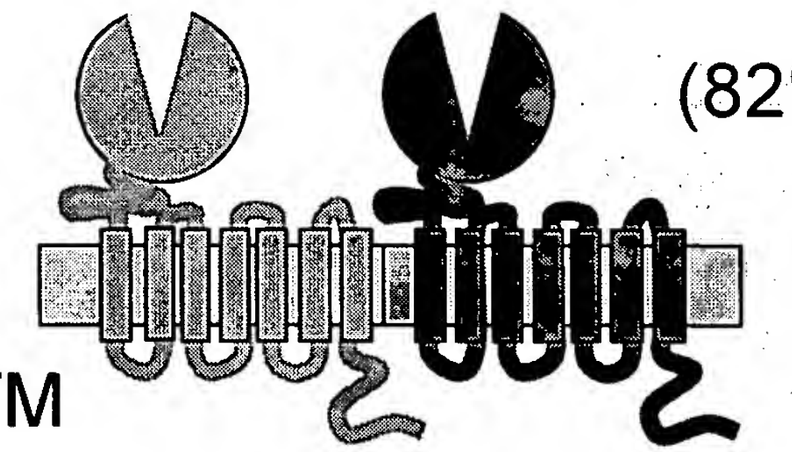
T1R1 T1R3



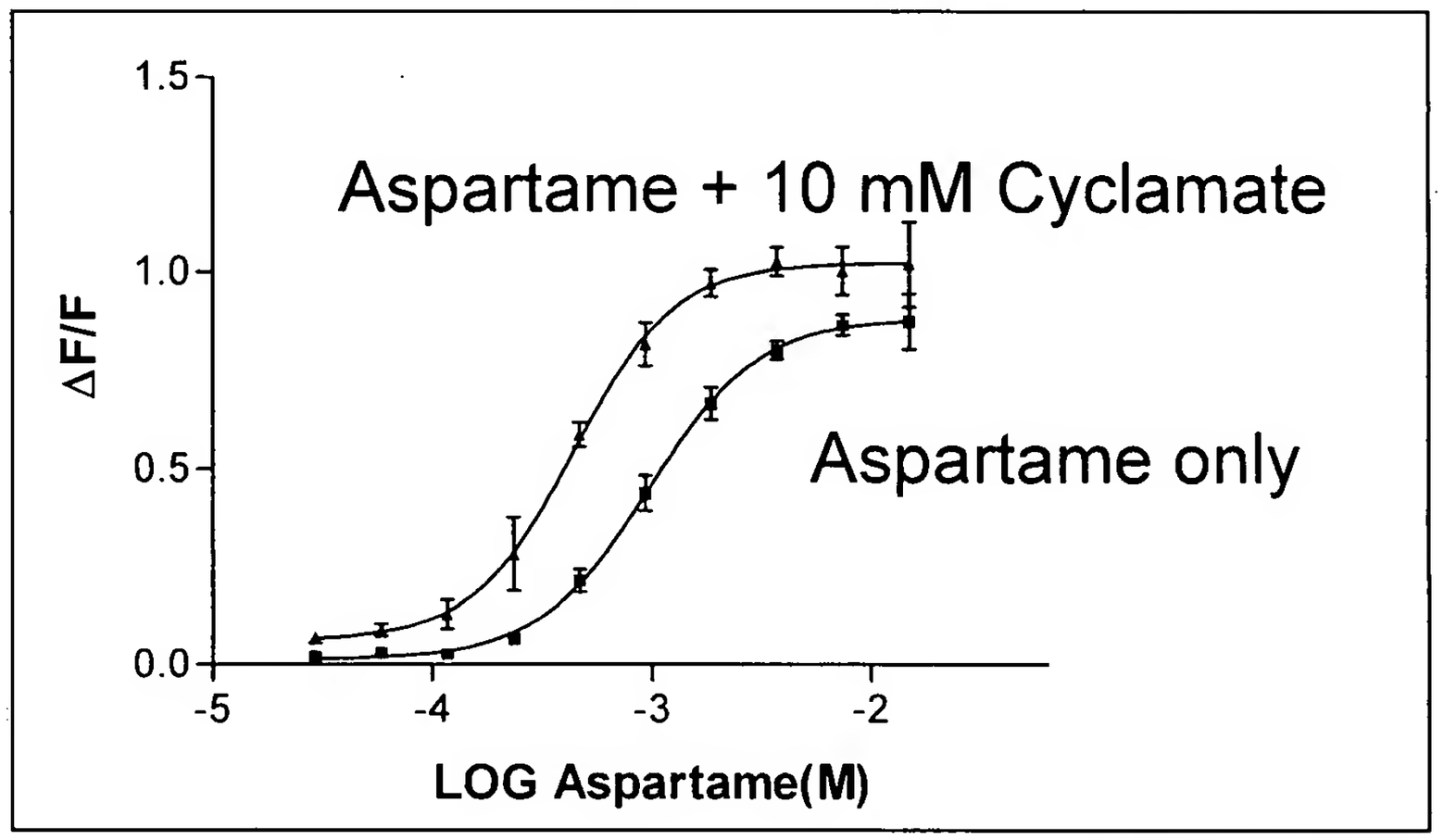
Umami Receptor

T1R2-ECD T1R3

T1R1-TM



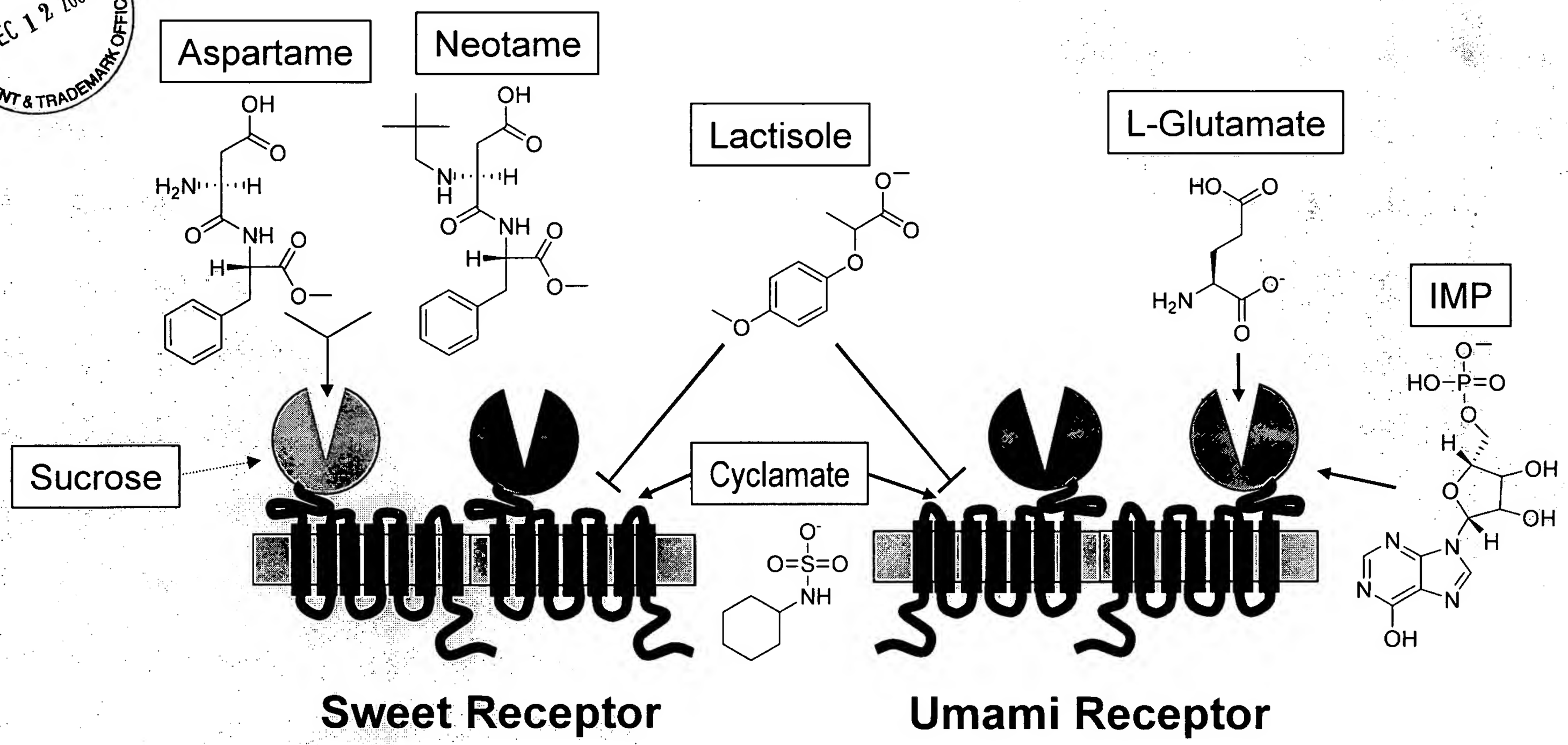
Domain Swap Receptor (82% identical to T1R2/3



Hybrid receptor also binds sucrose

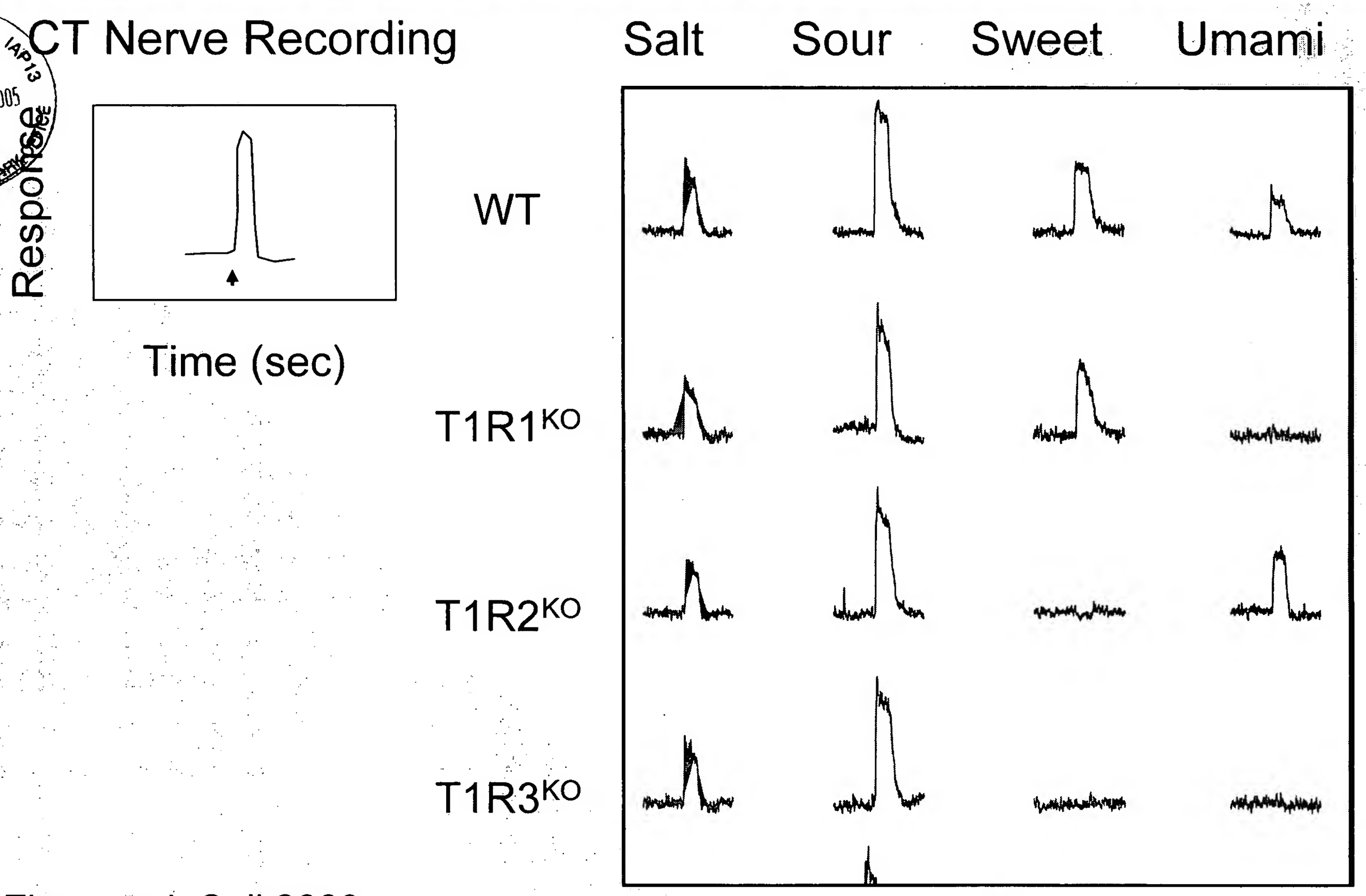
Senomyx, Inc.

Summary of Binding Sites on Heteromeric Taste Receptors



Senomyx, Inc.

Validation of Sweet and Umami Receptors By Gene "Knock-outs" in Mice

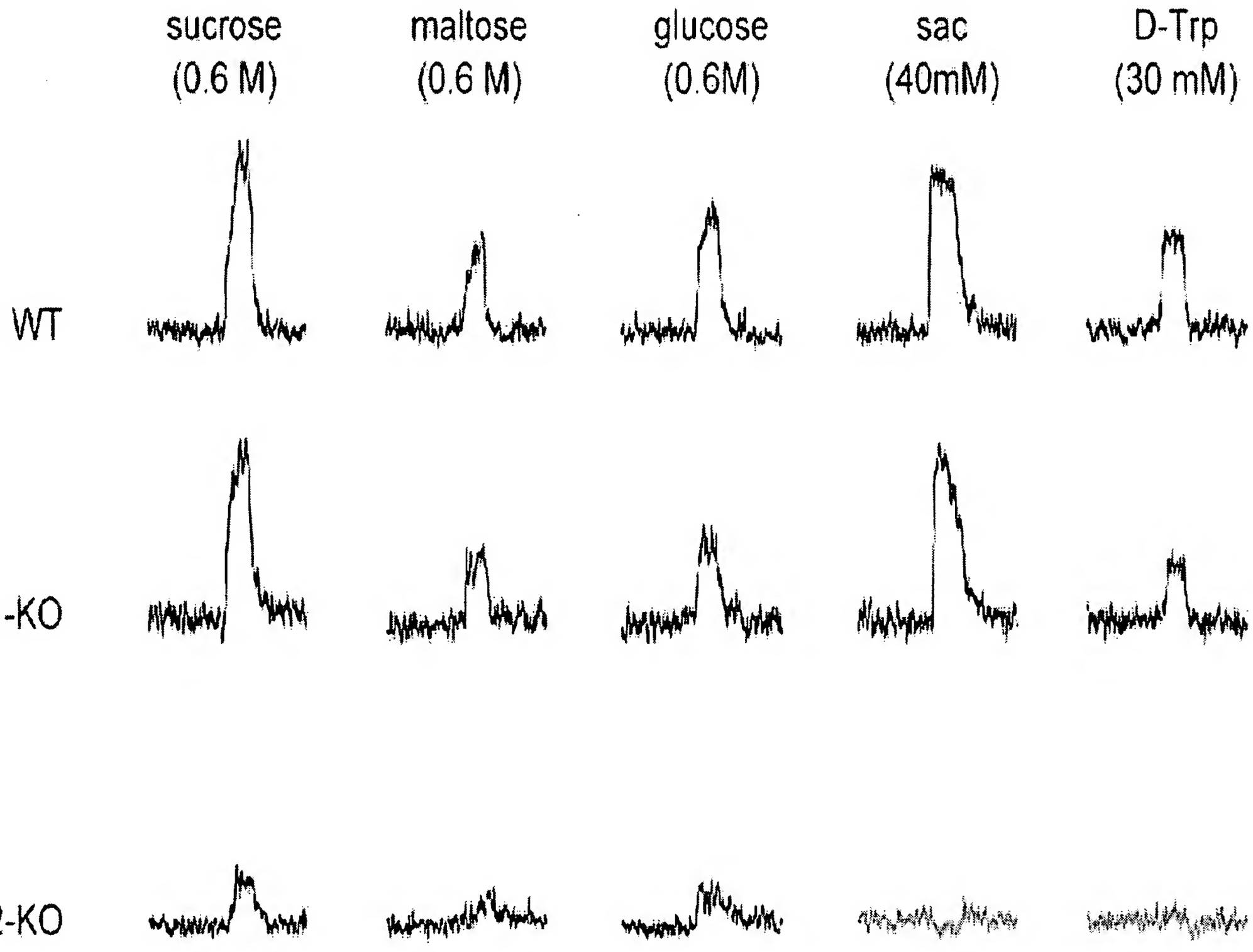


Zhao et al. Cell 2003

Senomyx, Inc.

Mice Containing Only T1R3 Respond to High Levels of Carbohydrate Sweeteners

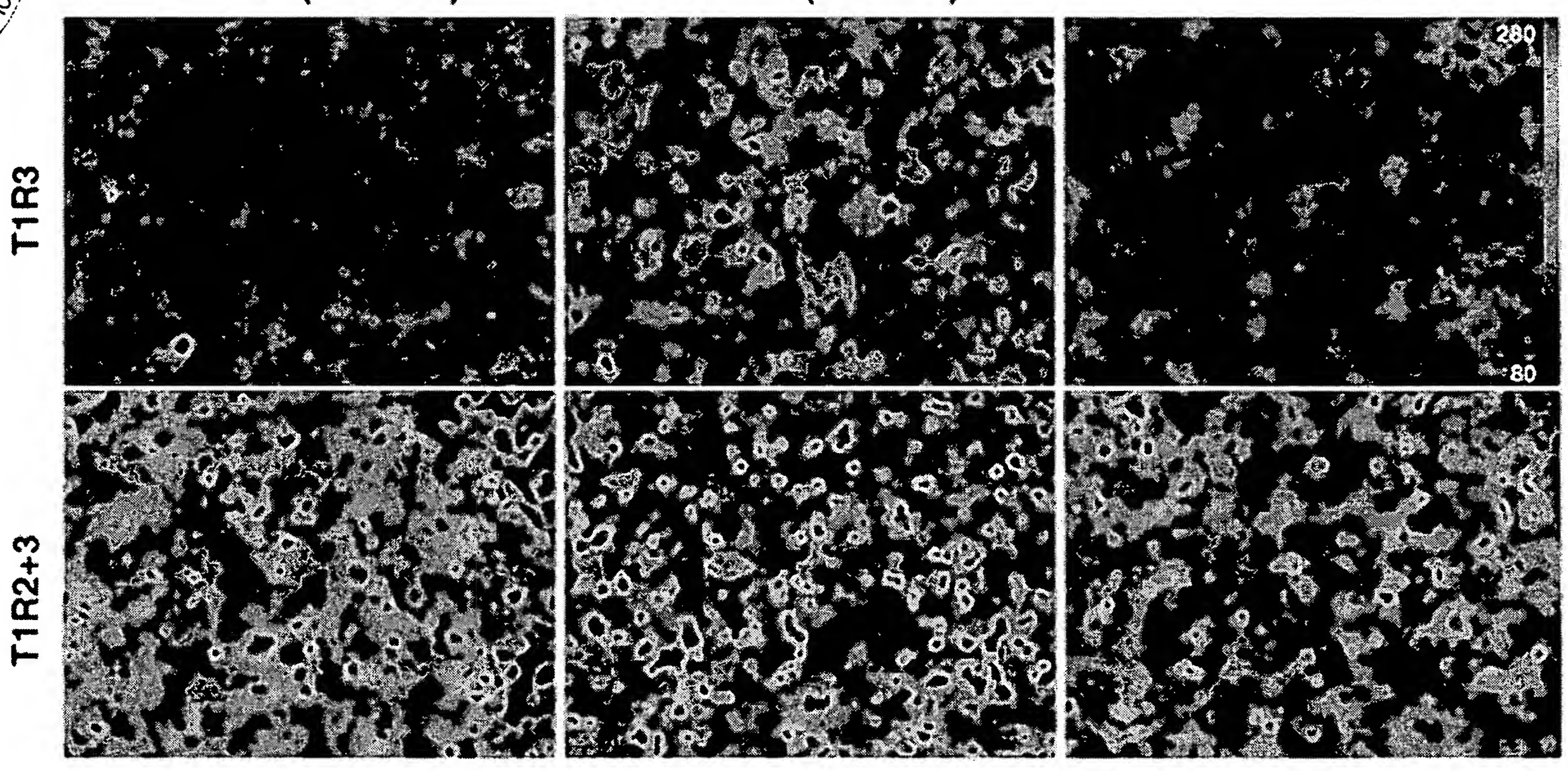
a



Zhao et al. Cell 2003

Senomyx, Inc.

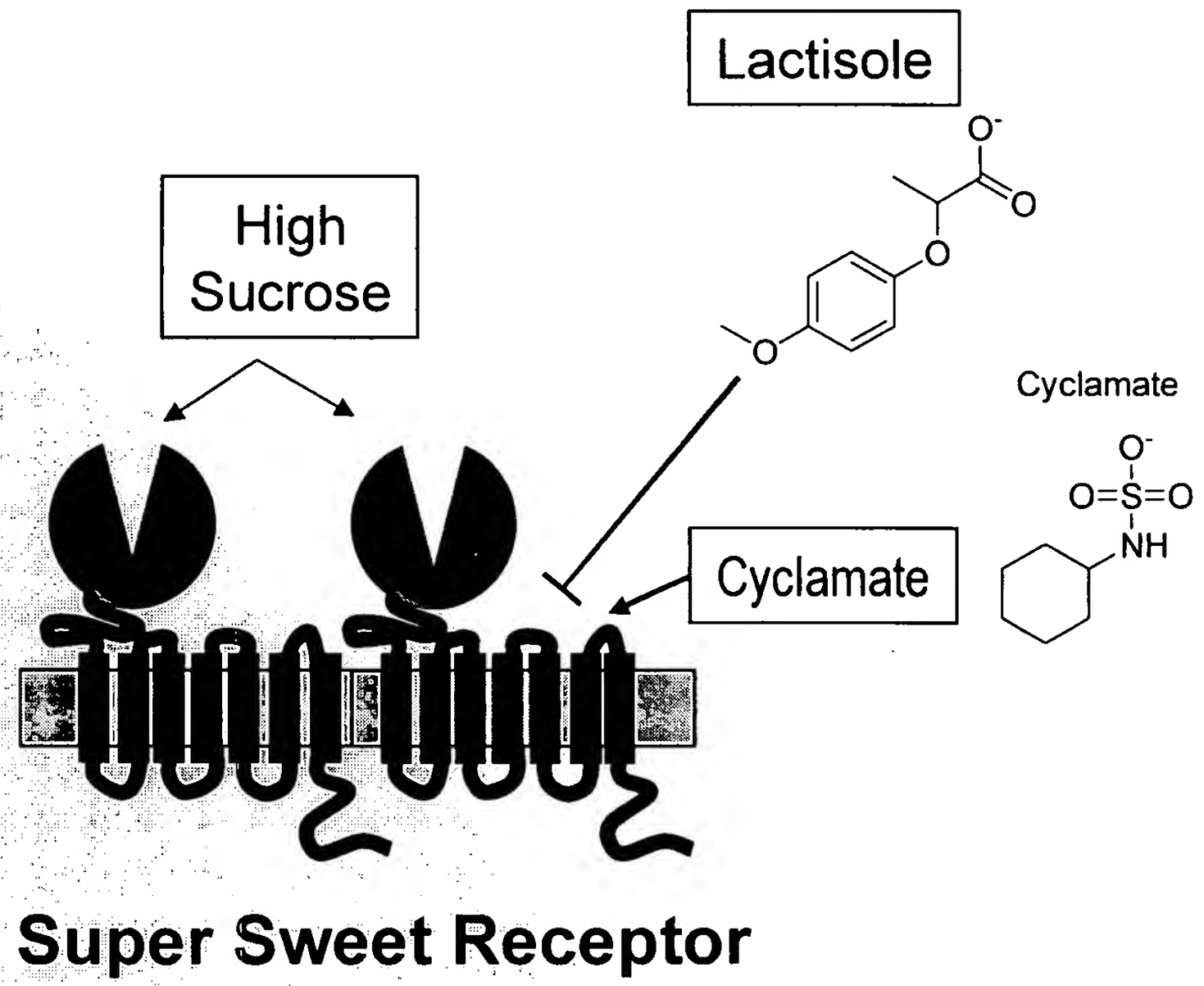
Cells Expressing Only T1R3 Respond to High Levels of Sucrose



Zhao et al. Cell 2003

Senomyx, Inc.

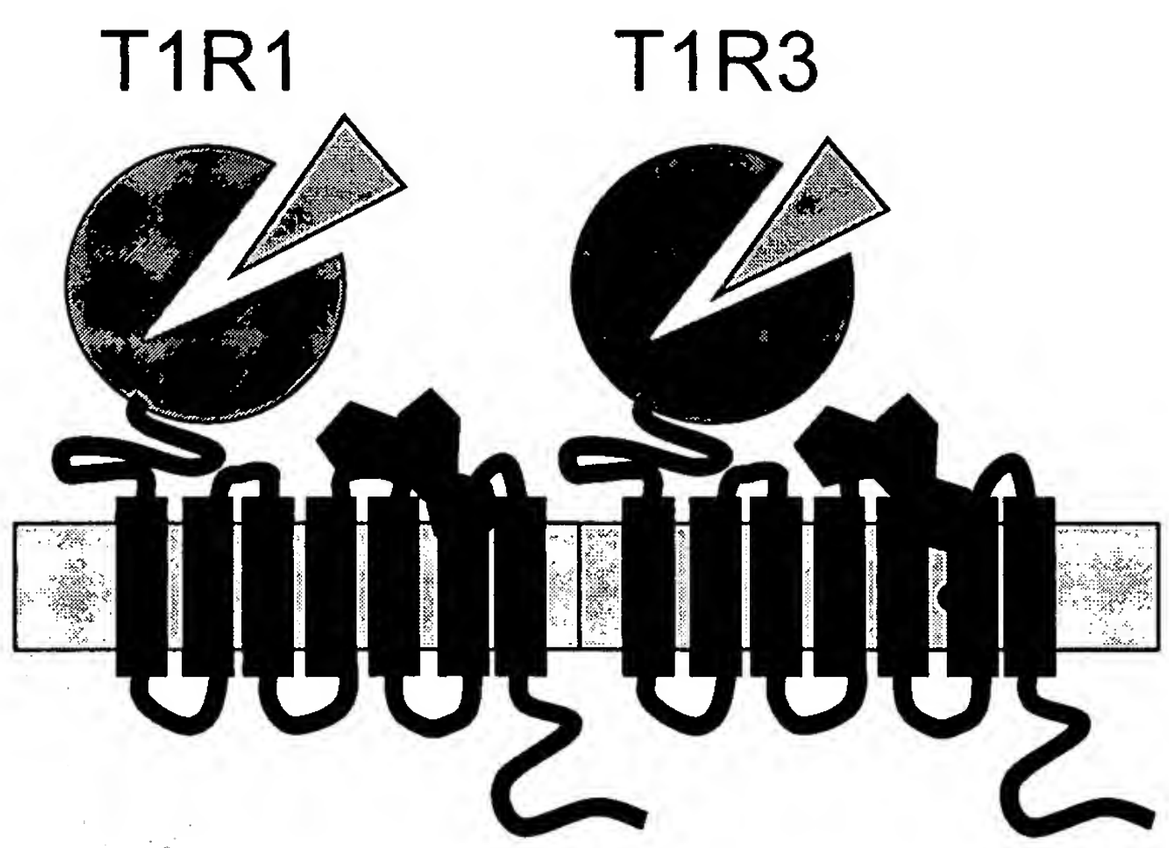
Summary of Binding Sites on a T1R3 Homodimer



Senomyx, Inc.

Using the Umami Receptor as a Model for Sweet Enhancers

Umami Receptor



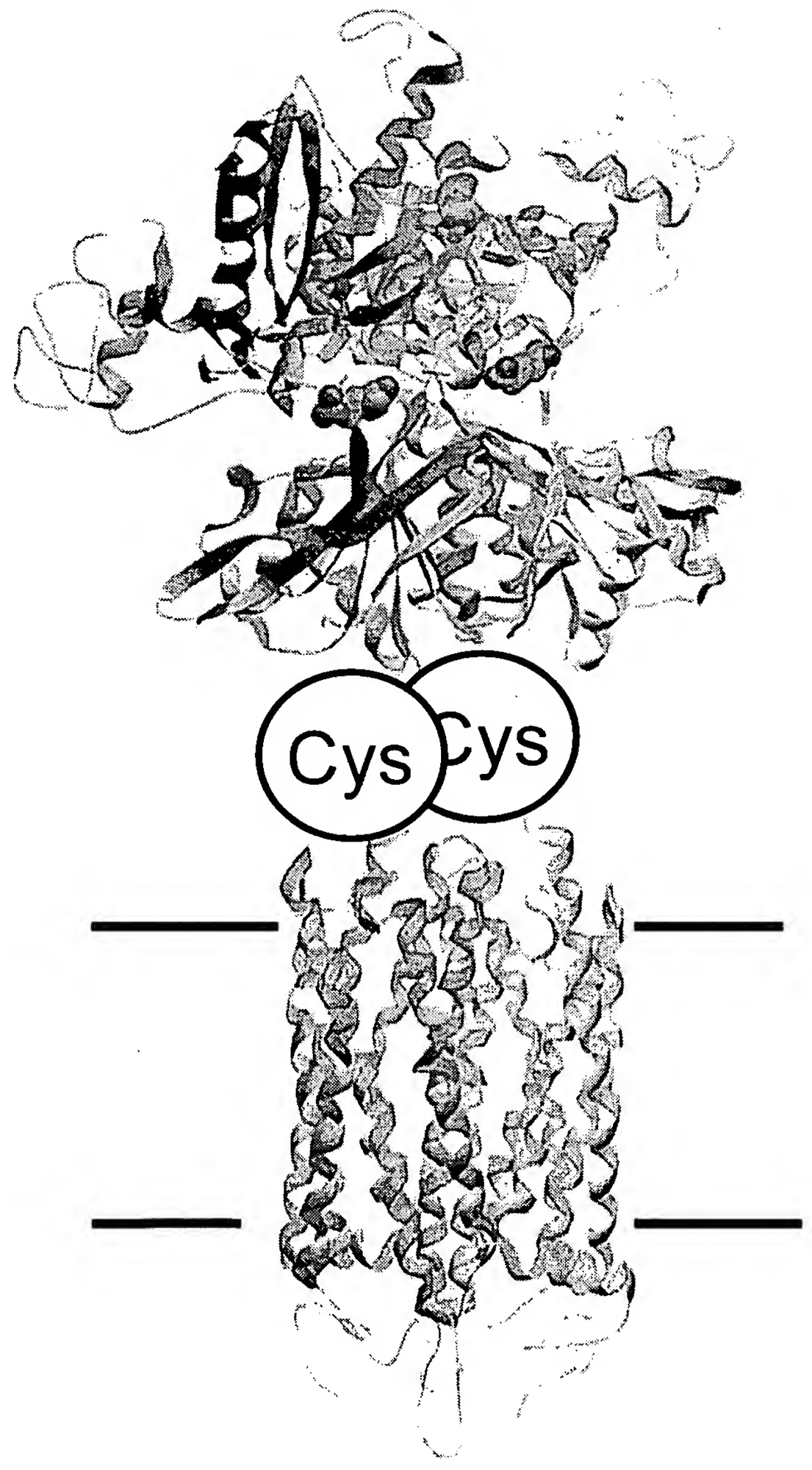
Agonists = Glutamate, Aspartate
Allosteric modulators = IMP, GMP, AMP

Activation Mechanism of Class C GPCRs

Venus flytrap module

Cystein-rich domain

Heptahelical domain

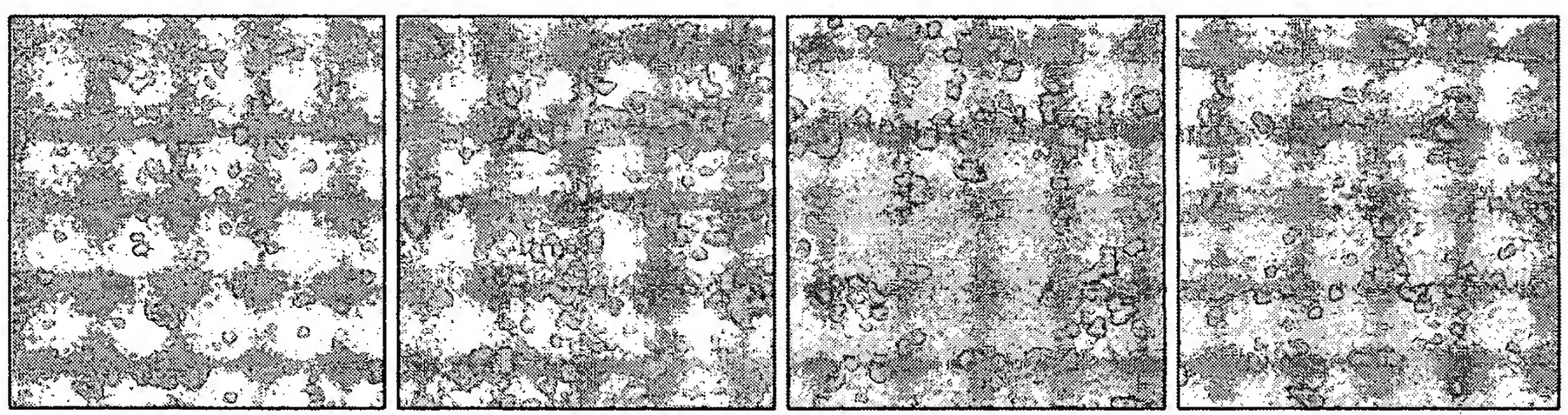


Active

Courtesy of Dr. Jean-Philippe Pin
Laboratory for Functional Genomics
Department of Molecular Pharmacology
CNRS UPR2580 - Montpellier, France.

Senomyx, Inc.

Ligand Specificity of Sweet Receptors



*Xu et al PNAS (*2004)

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by Dennis Crouch, patent attorney at McDonnell Boehnen Hulbert & Berghoff LLP.

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Dennis Crouch
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Jun 14, 2005

PTO Board: Disclosure of Sequence Enables at least 5% of Natural Variance.

Ex parte Bandman, No. 2004-2319, (BPAI 2005)

By Donald Zuhn

In an appeal from a final rejection, the PTO Board reversed rejections based on both the written description and enablement requirements of 35 U.S.C. § 112, first paragraph, and entered a new ground of rejection under 35 U.S.C. § 112, second paragraph one of the claims. (U.S. Application No. 09/915,694).

Pointedly, the Board found that claims directed to a naturally occurring amino acid (or polynucleotide) sequence at least 95% identical to the disclosed amino acid (or polynucleotide) sequence were enabled and met the written description requirement.

Claims 3 and 12 of the '694 application, which were representative of the subject matter on appeal, recite, inter alia, an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1 (claim 3) and an isolated polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2 (claim 12).

The Examiner had rejected these claims for failing to comply with the written description requirement, asserting that the

November 2005

October 2005

September 2005

August 2005

July 2005

June 2005

May 2005

April 2005

March 2005

February 2005

specification provides only a single representative species - the polynucleotide of SEQ ID NO: 2, and fails to disclose any structure-function relationship in this species. The Examiner had also rejected the claims for failing to comply with the enablement requirement, asserting that because the specification does not teach the specific amino acids and structural motifs in the proteins encoded by the claimed polynucleotides that are essential for protein activity (specifically, malate dehydrogenase activity), the amount of experimentation required to make the claimed polynucleotides was undue. Appellants contended that because the claims at issue recite polynucleotides having a naturally occurring polynucleotide sequence, or that encode a polypeptide having a naturally occurring amino acid sequence, "through the process of natural selection, nature will have determined the appropriate amino acid sequences

Regarding written description, the Board noted that "[t]he written description requirement . . . does not require a description of the complete structure of every species with a chemical genus." The Board also compared the circumstances of the instant case with those faced by the Federal Circuit in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002). In *Enzo Biochem*, the Federal Circuit determined that an "[a]dequate written description may be present for a genus of nucleic acids based on their hybridization properties, 'if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar.'" (citing *Enzo Biochem*). In the instant case, the Board determined that the genus of molecules defined by the claims was similarly limited and reversed the Examiner's written description rejection.

With regard to the enablement rejection, the Board disagreed with the Examiner's assertion that in order to satisfy this requirement, the specification must provide guidance regarding the specific amino acid residues that are tolerant to change

without affecting malate dehydrogenase activity. Instead, the Board deemed persuasive Appellants' argument that because the claims were limited to naturally occurring sequences, nature will have determined the amino acid residues that are tolerant to change (i.e., naturally occurring variants will presumably retain malate dehydrogenase activity). In particular, in reversing the Examiner's enablement rejection, the Board determined that the Examiner had not provided sufficient evidence that a naturally occurring polypeptide that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 or a polypeptide encoded by a naturally occurring polynucleotide sequence that is at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2 would not retain malate dehydrogenase activity.

Although the Board reversed both the written description and enablement rejections, it also entered a new ground of rejection for claim 12 under 35 U.S.C. § 112, second paragraph. The Board found that the specification provided no guidance that would allow one of ordinary skill in the art to determine, with a reasonable degree of confidence, whether a polynucleotide sequence that is at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2 occurs naturally. The Board concluded that the metes and bounds of claim 12 were unclear, and therefore, that the claim was indefinite.

> *NOTE*: Attorney Donald Zuhn is a true expert in cutting edge biotech patent law and practices both prosecution and litigation at McDonnell Boehnen Hulbert & Berghoff LLP in Chicago. [Brief Biography].

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